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Can we depend on case management to prevent re-establishment of *P. falciparum* malaria, after local interruption of transmission?

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ABSTRACT

Recent declines in malaria burden in many parts of the world have prompted consideration of how interruption of *Plasmodium falciparum* transmission could be maintained, if achieved, and notably whether large-scale vector control could be replaced with surveillance. This information is essential for elimination feasibility assessments and planning. The risk of re-establishment of transmission depends mainly on vectorial capacity (receptivity), likely to rebound once vector control is removed, the rate of importation of infections (vulnerability), the capacity to detect and treat infections and the level of immunity in infected individuals. Timely detection and removal of new infections is likely to be critical to prevent re-establishment of transmission. We assess, through mathematical modeling and simulation, which levels of case detection and treatment (case management) are required to prevent re-establishment of transmission of *P. falciparum* after local interruption of transmission has been achieved, in settings with varying receptivity and vulnerability. We find that, even at rather low levels of receptivity, case management alone cannot reliably prevent re-establishment of *P. falciparum* malaria transmission in the face of medium to high importation rates. Thus, if vector control is to be discontinued, preventing the importations by controlling transmission in source areas will generally be necessary for preventing reintroduction in such settings, and cannot be substituted by very high levels of case management coverage.

Background

Recent years have seen remarkable decreases in morbidity and mortality due to *Plasmodium falciparum* malaria in a range of settings across Sub-Saharan Africa. These decreases have been achieved primarily by the application of effective vector control tools, such as indoor residual spraying (IRS) and insecticide-treated nets (ITNs), and the introduction of artemisinin combination therapies (ACTs) (Barnes et al., 2009; Bhattarai et al., 2007; Ceesay et al., 2008). Such successes, which have been made possible by increased donor commitment to malaria control, have prompted national health policy-makers and their partners to consider how interruption of transmission could be maintained, if achieved (Malaria Elimination Group, 2009).

Evidence suggests that in some areas with a relatively low endemicity, local transmission could be (Hay et al., 2008), or may already have been (John et al., 2009), interrupted. In such places, for example the Kenyan highlands and Zanzibar, vector control was critical to bringing about substantial decreases in transmission and continues to be widely applied. However, it is likely to be difficult to sustain the will to maintain high levels of these interventions, particularly after malaria has ceased to be a public health problem (Feachem and Sabot, 2008). Policy makers will need guidance on when it is safe to scale down large-scale vector control operations aimed at achieving interruption of transmission and on when to proceed with a policy that relies mostly on surveillance. Maintenance of transmission interruption without large-scale vector control has been possible in several areas with moderate endemicity levels, such as Reunion Island (Girod et al., 1995) and Singapore (Lee et al., 2009). In other places, such as Mayotte in the Comoros Islands, interruption of *P. falciparum* transmission has proved elusive even when it seemed imminent, despite intensive control efforts, and it seems that vector control will need to be maintained to prevent resurgence of malaria (Rebaudet et al., 2010). Understanding malaria resurgence risks is of critical importance to malaria control programmes when setting objectives and planning malaria strategies.

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In closed systems, interruption of transmission would be maintained automatically once achieved. However, in reality, human populations are connected to each other, and as long as local vectors have sufficient capacity to transmit malaria, local transmission can be reintroduced through immigration of infected people or infective mosquitoes. The greater the magnitude of this immigration, the more likely malaria transmission will resurge, all else equal. Evidence indicates that current control strategies, even applied at very high coverage, will be insufficient to interrupt transmission in much of Sub-Saharan Africa (Ferguson et al., 2010), so importation of infections will remain a major challenge for the foreseeable future for countries in the region which seek to maintain local interruption of transmission.

Health systems which deploy methods for timely detection and removal of imported infections can prevent re-establishment of transmission. For instance, Singapore, which reported elimination of malaria in 1982, saw a large cluster of imported *P. falciparum* malaria infections in 2005, but local onward transmission was prevented through early diagnosis, treatment and screening (Kang et al., 2007). Likewise, in the United States of America, outbreaks of locally transmitted malaria have been detected and contained on several occasions since certification of the country's malaria-free status (Mali et al., 2010).

Individuals can be infected with malaria, and capable of transmitting the disease, without showing clinical symptoms. Intervention strategies based on case detection and treatment target individuals with clinical disease, whereas others, such as mass drug administration or screening and treatment, include individuals without signs of illness. Although the latter types of approaches may identify a larger proportion of infections, screening or diagnosis with methods appropriate for use in the field, notably rapid diagnostic tests or microscopy, may still miss a significant number of infections with low or sub-patent parasite densities (Bousema et al., 2010; Harris et al., 2010). These types of approaches may also be less sustainable long-term, because of their costs and organizational requirements, potential to accelerate development of drug resistance, and refusal of healthy individuals to participate in repeated screenings (von Seidlein et al., 2003; von Seidlein and Greenwood, 2003; White, 2008).

After interruption of transmission, individuals' naturally acquired immunity will decay in the absence of exposure to malaria. Although the mechanisms involved are poorly understood, this decay in immunity could be expected to influence re-establishment of transmission in two ways. First, an infected individual with a lower anti-parasite immunity is more likely to be infective to mosquitoes. Second, an infected individual with a lowered immunity is more likely to show clinical symptoms and thus, given access to appropriate care, to be treated promptly, reducing the parasite reservoir. Both these effects need to be considered in assessing the likely outcomes of different strategies.

The vectorial capacity is the capacity of the combined vector populations present in an area to transmit disease agents, expressed as the potential number of inoculations per time unit originating from an infective person with no prior immunity. In the absence of major structural environmental or socio-economic changes, it is probable that, after withdrawal of large-scale vector control operations, the vectorial capacity will revert quickly to the same level as prior to control. As the vectorial capacity is difficult to measure, the pre-intervention entomological inoculation rate (EIR) may be a good proxy measure for the receptivity.

The risk that transmission will re-establish in an area thus depends mainly on the local receptivity, or vectorial capacity, the local vulnerability, or infection importation rate (IIR), the capacity to detect and treat infections, and the level of immunity in infected individuals. The purpose of this paper is to assess, through mathematical modeling and simulation, which levels of case detection and treatment (case management) are required to prevent re-establishment of transmission of *P. falciparum* after local interruption of transmission has been achieved, in settings with varying receptivity and vulnerability.

Methods

Individual-based stochastic simulation models of the biology and epidemiology of *P. falciparum* malaria were developed to study long-term impacts and cost-effectiveness of intervention strategies, and have been described elsewhere (Smith et al., 2006a, 2008). Briefly, there is a simulated population of humans who are updated at each five-day time step via model components representing new infections, parasite densities, acquired immunity, uncomplicated and severe episodes, direct and indirect malaria mortality, infectiousness to mosquitoes, and case management. Simulated immunity to asexual parasites, derived from cumulative exposure to both inoculations and parasite densities and maternal immunity, acts mainly by controlling parasite densities (Maire et al., 2006a). The probability of a clinical attack of malaria depends on the current parasite density and a pyrogenic threshold (Smith et al., 2006b). Severe malaria comprises two categories of episodes: those that occur as a result of overwhelming parasite densities, and those that arise when an uncomplicated malaria episode coincides with non-malaria co-morbidity. Mortality can be either direct (following severe malaria) or indirect (uncomplicated malaria in conjunction with co-morbidity, or during the neonatal period as a result of maternal infection) (Ross et al., 2006b). There is also a model of the dynamics of malaria in mosquitoes (Chitnis et al., 2008).

Infectivity of hosts to mosquitoes at a given time point is modeled as a function of asexual parasite densities 10, 15 and 20 days previously, allowing for the delay resulting from the time course of gametocytemia (Ross et al., 2006a). Effective treatment completely clears parasites by the next time step, ending the infection, while ineffective treatment has no impact on asexual parasite densities. By clearing asexual parasites, case management renders individuals uninfectious to vectors at later time points. Given sufficiently high case management coverage, this lowered infectivity translates into a future reduction in EIR. We do not model the effects of drug treatment on gametocytemia.

Previous studies using these models (Maire et al., 2006b; Penny et al., 2008) focused on settings of medium to high transmission intensity, for which the model outcomes could be presumed to be insensitive to importation of infections. We have now extended these models to include importation of infections, and applied them to low and medium transmission settings.

We used three different pre-intervention EIRs of two, 20, and 50 inoculations per adult per annum (ibpapa), with a pattern of seasonality as observed in Namawala, Tanzania (Smith et al., 1993). The infection status and immune status at the start of the simulation are determined by exposing the simulated population to the same annually recurring pattern of inoculations for a lifetime-long burn-in at the start. The level of case management coverage was set at zero during the burn-in period in all simulations in order to ensure that the simulated vectorial capacity was the same across all scenarios. Case management coverage was changed to the appropriate level at the beginning of the main simulation.

We used a population size of 1000, with underlying demography based on East African life tables (INDEPTH Network, 2002). In our simulations, to interrupt transmission, we applied mass drug administration at 100% coverage and cleared all infections from vector mosquitoes over a period of 30 days at the beginning of year 2. These interventions are not intended to be realistic, but were a convenient way to locally eliminate malaria in our simulations. Achievement of such high coverage of mass drug administration

Table 1
Descriptions of model variants and predicted odds ratio that transmission remains interrupted for each model variant relative to the base model, at pre-intervention EIR of 2 and 20 ibpapa.

Model identifier	Description	Half-life of decay (years)		Odds ratio, EIR = 2	95% confidence interval		Odds ratio, EIR = 20	95% confidence interval	
		$t_{1/2} = -\ln(2)/\alpha_b$	$t_{1/2} = -\ln(2)/\alpha_c$						
R0125	Fixed decay in immune proxies	∞	10[a]	4.57	4.02	5.21	1.47	1.27	1.71
R0132	Estimation of decay in immune proxies	∞	14	4.31	3.79	4.90	1.29	1.11	1.49
R0115	Fixed decay in effective cumulative exposure	10[a]	∞	4.17	3.67	4.74	1.29	1.11	1.50
R0133	Estimation of both decay parameters	250	19	3.89	3.42	4.42	1.37	1.18	1.59
R0131	Estimation of decay in effective cumulative exposure	1187	∞	2.42	2.14	2.74	1.36	1.17	1.58
R0065	Mass action: $E_a(i,t)$ varies between and within hosts	∞	∞	2.18	1.93	2.47	1.89	1.63	2.20
R0670	Heterogeneity in susceptibility to comorbidity	∞	∞	2.03	1.80	2.30	1.22	1.05	1.41
R0063	Mass action: $E_a(i,t)$ varies mainly between hosts	∞	∞	1.86	1.64	2.10	2.04	1.75	2.37
R0121	Fixed decay in immune proxies	∞	1000[a]	1.63	1.45	1.84	1.18	1.02	1.37
R0068	Mass action: $E_a(i,t)$ varies mainly within hosts	∞	∞	1.44	1.27	1.62	1.53	1.32	1.78
R0111	Fixed decay in effective cumulative exposure	1000[a]	∞	1.30	1.15	1.46	1.14	0.98	1.33
R0674	Uncorrelated heterogeneities in access to treatment and susceptibility to comorbidity	∞	∞	0.63	0.56	0.71	1.04	0.89	1.21
R0678	Heterogeneity in access to treatment	∞	∞	0.56	0.50	0.63	0.87	0.75	1.02

$E_a(i,t)$: the expected number of entomological inoculations, adjusted for age and individual factors.
α_b: decay applied to the two measures of the effective cumulative exposure.
α_c: decay applied to the function representing the immune status.
[a] These parameters were fixed, in other models the decay parameters were estimated. Decays shorter than the shortest fixed values gave unacceptable fits to the data.

would be nearly impossible in a real-life setting, nor do we consider the mechanism by which all infections could be simultaneously cleared from vector mosquitoes.

The case management component (Tediosi et al., 2006) models a health system using ACT. Individuals with uncomplicated malaria were assigned a probability of accessing treatment over the next five-day period, expressed as percent coverage, which was varied between 0% and 100% at 10% intervals. These probabilities were constant over the entire time period of the simulation. We considered only case detection and treatment based on clinical symptoms. Compliance to the drug was set at 90% (Fogg et al., 2004), and the drug was assumed to be 98% effective. In patients who did not comply, the drug was assumed to have an effectiveness of 20%. All severe cases were assigned a probability of receiving treatment as an inpatient of 48%, and parasites were cleared in all hospitalized cases who survived (Tediosi et al., 2006).

Imported infections were simulated by assigning infections to individuals in the population stochastically every 30 days at a constant average rate throughout the simulation period. No infected mosquitoes entered the local system. The rate of imported infections was Poisson distributed with mean of 0, 0.02, 0.2, 2, or 20 imported infections per 1000 persons per annum. These rates compare to estimates of infection importation rates in Zanzibar ranging from 2 to 8 infections per 1000 inhabitants per annum in 2008 (Malaria Elimination Group, 2009; Tatem et al., 2009) and cases reported as imported in South Africa from 1981 to 1999 ranging from about 0.02 to about 0.17 per 1000 population (Craig et al., 2004). The IIR of 0 was included as a reference scenario to check that transmission had indeed been interrupted by mass drug administration and clearing infections from vectors.

We evaluated the impact of all possible combinations of these scenarios on the number of malaria episodes expected over the last 14.75 years of the simulations. For each IIR, we chose a threshold number of cases over the 14.75-year period after interruption of transmission above which we considered transmission to have re-established. This threshold was calculated by taking the 97.5 percentile of the Poisson distribution of the number of imported cases that would be expected over the period, and multiplying this by 3, thus allowing each imported infection to give rise to a maximum of 2 secondary infections before classifying the simulation as one where transmission was re-established. The reason for using the 97.5 percentile was to establish a very generous threshold for re-establishment. If malaria is considered to have re-established under these conditions, it is not likely to be kept out under more strict definitions.

We assessed the uncertainties in model predictions resulting from stochastic variation and from the assumptions in our model formulations by using 100 different seeds for the random number generator and an ensemble of 14 model variants as described in Table 1. The ensemble consists of a base model, used in previous publications (Maire et al., 2006b; Penny et al., 2008), and thirteen variants on that model, with each one representing a different set of assumptions about malaria transmission and epidemiology. The motivation for using model ensembles is to assess how our understanding of a particular phenomenon is affected by uncertainty in model assumptions. Our ensemble of stochastic simulation models of malaria epidemiology incorporates different assumptions about decay of immunity and about heterogeneities in exposure, co-morbidity and access to treatment (Smith et al., in press).

While the base model assumes that, in a given transmission setting, entomological exposure depends only on age, the model variants for heterogeneities in exposure include random variation in the availability of the human host to mosquitoes. Thus, the expected number of entomological inoculations is additionally a function both of the individual and of log-normal noise. Three different parameterisations were considered—*R0063* assigns most variation to be inter-host, *R0068* assigns the variation predominantly to within host variation, and *R0065* is intermediate.

The model for natural immunity used in the base model, developed primarily for simulating the epidemiology of malaria in endemic settings, does not allow for any decay of immunity in the absence of exposure. To allow for such decay, the base model was

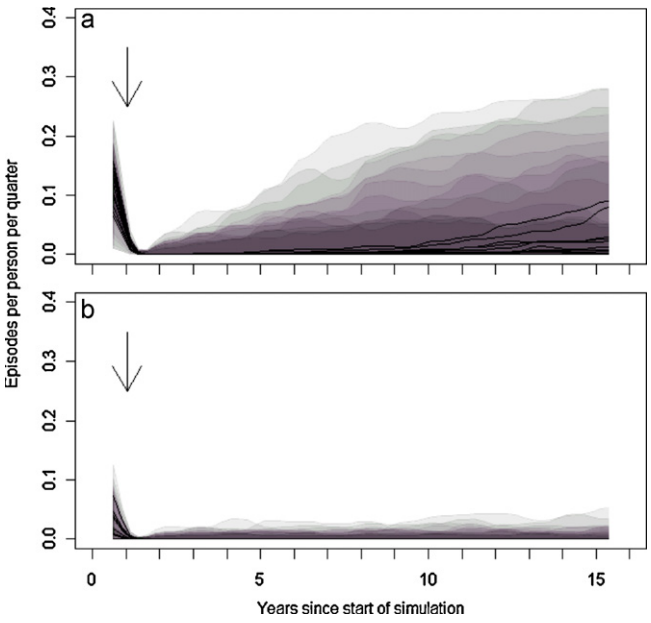

Figure 1. Simulated clinical incidence by model variant with 20% (a) and 80% (b) case management coverage, at IIR = 2 per 1000 persons per annum, and at a pre-intervention EIR of 2 ibpapa. Black lines: model variant medians; gray shading: 95% probability interval around each median. Results are smoothed to remove the effect of seasonality. The arrow indicates the time point where transmission is interrupted with mass drug administration and clearing infections from vectors.

extended by two alternative algorithms. In both cases, the model variants were parameterised so that in the absence of new exposure, the decayed value is some fixed proportion of that at the previous five-day time step. The half life of the decay is either fixed at 10 or 1000 years or estimated during the model fitting process.

Finally, the model variants for heterogeneities in co-morbidity and access to treatment assign each simulated individual a status for each of the two kinds of heterogeneity at birth, which they carry throughout their life, structured in each case so that 50% of the population are assigned to each of the high and low status categories, with the values in the base model multiplied by either 1.8 or 0.2. Two of the model variants simulate these heterogeneities singly, while the third simulates both, where they are assigned to individuals independently of each other.

Analyses were conducted using R statistical software version 2.11.1 (R Development Core Team, 2010).

Results

Fig. 1 illustrates the use of model ensembles to simulate clinical episodes over time, in a setting with a pre-intervention EIR of 2 ibpapa. Model variant medians for simulated incidence post-intervention were higher at 20% (a) case management coverage than at 80% (b), indicating the effect of higher case management coverage in reducing transmission. In these scenarios, where IIR = 2 per 1000 persons per annum, the higher case management coverage level seems to prevent the resumption of transmission in most simulations, in contrast to the lower case management coverage level. There was a much larger variation among model variant outcomes post-intervention at the lower case management coverage level.

Fig. 2 depicts the proportion of model variant simulations in which transmission remained interrupted as a function of case management coverage at different IIRs. In the lowest transmission setting with a pre-intervention EIR of 2 ibpapa (Fig. 2a), there was a positive relationship between case management coverage and the proportion of simulations in which transmission remained interrupted for all IIR levels except at 0.02 imported infections per 1000 persons per annum. At IIR = 0.2 per 1000 persons per annum, 60% case management coverage resulted in maintenance of interruption of transmission in 86% of simulations of the median model variant. At IIR = 2 and 20 per 1000 persons per annum, predicted success was much lower; at IIR = 2, at 60% case management coverage, transmission remained interrupted in only 66% of simulations of the median model variant, while at IIR = 20, transmission remained interrupted in only 15% of simulations of the median model variant at 60% case management coverage. At IIR = 0.2 and 2 per 1000 persons per annum, most of the benefits from increasing case management coverage seem to be gained at lower coverage levels; at 70% case management coverage, the imaginary curve through the median model variant results flattens off. As seen from the boxplot, variation in probability of success over the model variants was relatively large at the IIR levels 2.0 and 20. At the lowest IIR, 0.02 per 1000 persons per annum, case management coverage level had little effect on the probability of success; however, at this low IIR level, the probability that no infections were imported during the observation period in a simulation was 74%. At IIR = 0.2 per 1000 population per annum, this probability was approximately 5%.

In the higher transmission settings (Fig. 2b and c), at IIR = 0.2 per 1000 persons per annum, higher case management coverage slightly increased the proportion success in preventing re-establishment, but even with perfect passive case detection, transmission returned in at least half of simulations of the median model variant. In these settings, at IIR = 2 or 20 per 1000 persons per annum, interruption of transmission was never, or almost never, maintained.

Fig. 2 primarily serves to show the trends among case management coverage, IIR, and the proportion of simulations in which transmission remained interrupted, and where most model variants agreed and where there was a wider range in predictions. The median proportion of simulations in which transmission remained interrupted may be biased and should not be over-interpreted, as it is unclear how to weight the fourteen model variants to allow for plausibility, goodness of fit and correlations both in structure and parameter values.

In general, at low case management coverage, the model variants for heterogeneities in exposure resulted in a higher proportion of simulations in which transmission remained interrupted. At medium to high case management coverage, it was the decay of immunity model variants which resulted in a higher proportion. The model variants with heterogeneities in access to treatment usually resulted in a lower proportion of simulations in which transmission remained interrupted.

For each pre-intervention EIR, we fitted a logistic regression model to the probability of success in preventing re-establishment of transmission, with covariates in case management coverage, the natural logarithm of the infection importation rate, and each of the fourteen model variants as categorical variables. Backward stepwise regression showed that removing any of the independent variables from the model was found to significantly decrease the model's goodness of fit at the 95% confidence level, so all covariates were kept. We then tested for interaction between case management coverage and the natural logarithm of the infection importation rate. From the likelihood ratio test, the interaction term was found to be significant ($p < 0.001$), although it has only a slight effect.

The fitted relationships between case management coverage and the probability that transmission remains interrupted, for the base model and at different IIRs, are shown in Fig. 3a (EIR = 2 ibpapa) and Fig. 3b (EIR = 20 ibpapa). The figure at EIR = 50 ibpapa looks very similar to that at EIR = 20 ibpapa and is not shown. At EIR = 2 ibpapa, the odds ratio that transmission remains interrupted

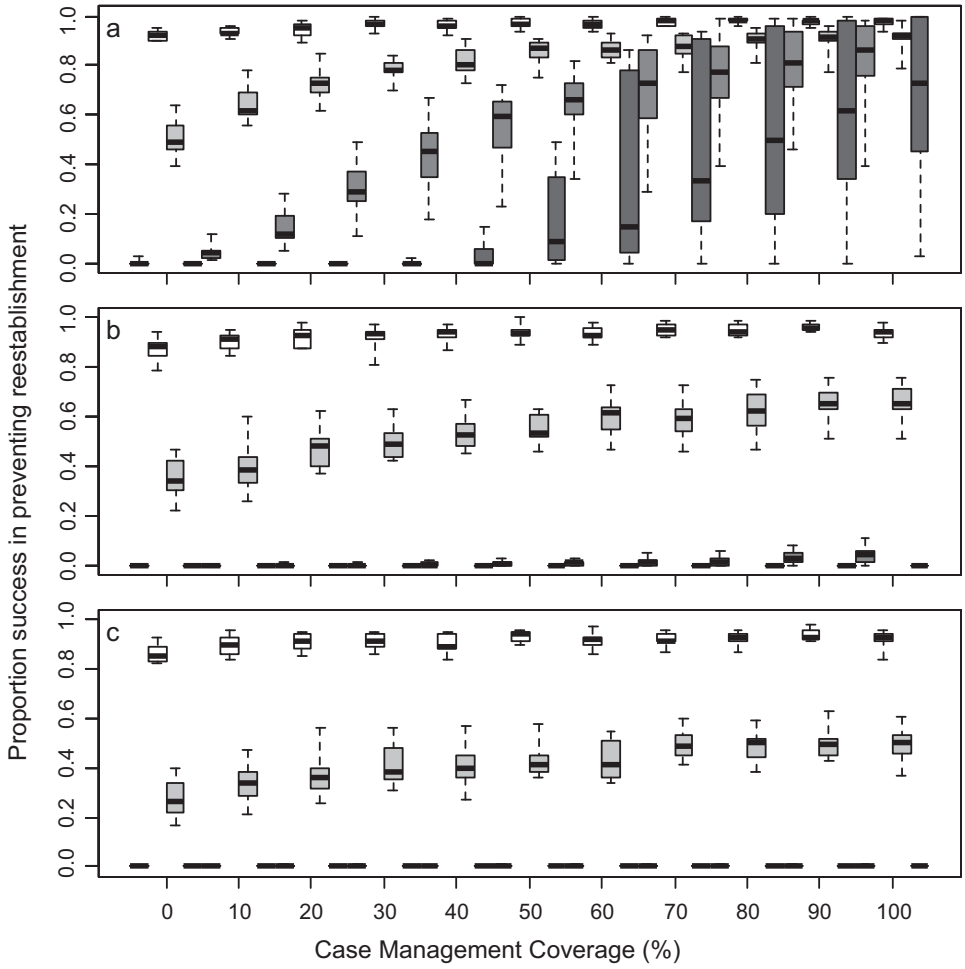

Figure 2. Boxplot (with the median, maximum, minimum, and interquartile ranges) of the proportion of simulations in which transmission remained interrupted, by model variant, at each case management coverage level and infection importation rate and at a pre-intervention EIR of 2 ibpapa (a), 20 ibpapa (b) and 50 ibpapa (c). Fill colours: white: IIR = 0.02, light gray: IIR = 0.2, medium gray: IIR = 2, dark gray: IIR = 20 imported infections per 1000 per annum.

associated with a tenfold decrease in IIR is 16.6 (95% CI: 15.6, 17.6). At EIR = 20 ibpapa, the corresponding odds ratio is 23.7 (95% CI: 21.5, 26.3).

Table 1 shows that, at a pre-intervention EIR of 2 ibpapa, the model variants which included decay of immunity with a shorter half-life were found to have a relatively large positive effect on the odds that transmission remained interrupted relative to the base model. By contrast, model variants R0674, which assumes uncorrelated heterogeneity in co-morbidity and access to treatment, and R0678, which assumes heterogeneity in access to treatment, were found to have a relatively large negative effect on the odds that transmission remained interrupted relative to the base model.

At the higher pre-intervention EIRs of 20 ibpapa and 50 ibpapa (not shown), the model variants had much smaller effects on the odds that transmission remained interrupted relative to the base model. This is evidenced by the much narrower range in the odds ratios. Moreover, in these transmission settings, it was the model variants that assumed heterogeneity in entomological exposure that had the largest positive effects on the odds that transmission remained interrupted.

Discussion

Although maintaining interruption of malaria transmission would bring benefits, it would also require reorientation of programmatic strategies, significant long term financial commitments, and major operational preparations. Therefore, the decision to pursue transmission interruption and prevention of re-establishment of transmission is not trivial. Prior to embarking on such a course a thorough evaluation of the likelihood of success, and what will be required to maintain it, is desirable.

Early detection and treatment of infections is critical to prevent onward transmission in the face of renewed vectorial capacity. However, our findings also suggest that, even where vectorial capacity is low, maintaining interruption of transmission is likely to require continued vector control at or above moderate levels of vulnerability (IIRs on the order of 0.2 per 1000 population per annum or higher). Even perfect passive case detection will fail to identify imported asymptomatic infections, which under these circumstances will be sufficiently numerous to result in a considerable probability of resumption of transmission. The chances that an imported infection is asymptomatic will depend on the immunity profile of the immigrant/visitor, which in these analyses was assumed to match that of the simulated population.

Statistical analysis revealed that modeled outcomes were sensitive to several of the model assumptions. At low pre-intervention EIR levels, decay of natural immunity is an important driver of whether or not interruption of *P. falciparum* malaria transmission can be maintained. This is because, as immunity decays, more infections are likely to be symptomatic, and therefore detectable and treatable by the passive case management system. Also, in the base model, individuals are assumed to have homogenous access to treatment and to be at similar risk of co-morbidity. In this analysis, introducing heterogeneities in these factors increased the risk

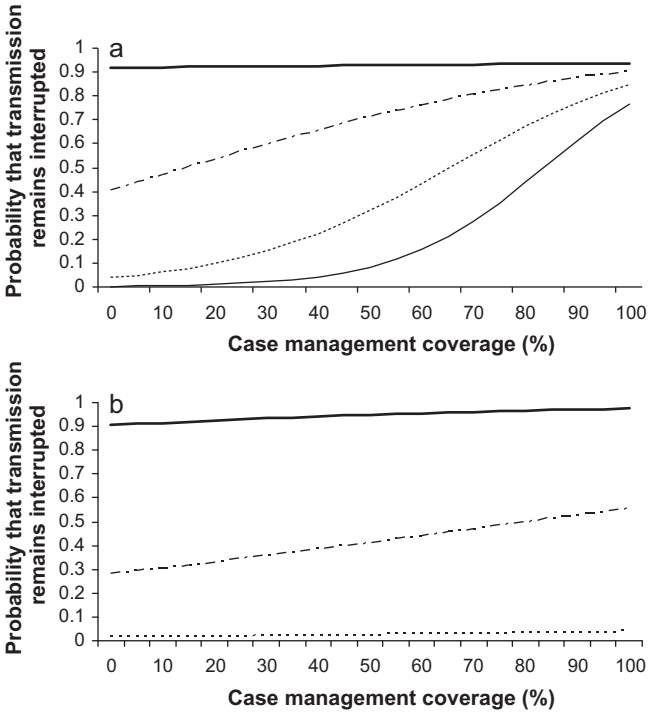

Figure 3. (a and b) Best-fitting regression model predictions for the probability that transmission remains interrupted, as a function of case management coverage and infection importation rate, at pre-intervention EIR of 2 (a) and 20 (b), using the base model. Thin line: IIR = 20, dotted line: IIR = 2, dashed line: IIR = 0.2, thick line: IIR = 0.02 imported infections per 1000 per annum.

of re-establishment. These findings suggest that areas with these kinds of differentials among population sub-groups may face specific challenges in maintaining transmission interruption.

In higher transmission settings, variations in these assumptions did not have as large an effect on the odds that transmission remained interrupted. At higher pre-intervention EIRs, the vectorial capacity is the dominant determinant of re-establishment. In these settings, immunity was much higher post-interruption than in the low-transmission setting, and thus even with decay, a large number of infections remain asymptomatic.

The perhaps counter-intuitive finding that the models assuming heterogeneity in force of infection had positive effects on the odds that transmission remained interrupted could be explained in several ways. First, if infections are concentrated in the same people, a given level of case management coverage will result in a higher proportion of infections being treated than if infections are spread more evenly across the population (because a single treatment will terminate all co-infections in that host). Second, this finding may be due to the way we have constructed our outcome variable. Where certain individuals have higher availability to mosquitoes than others, this may result in a lower number of episodes (as multiple infections can give rise to only one episode at a time).

There are several factors that are likely to affect the probability of success in preventing re-establishment which were not considered here. Characteristics of the population under consideration, for example the size of the population and the degree of interaction between individuals, were not studied. Interruption of transmission is easier to achieve and maintain in smaller populations than in large ones, *ceteris paribus*, as re-introduction of transmission is an infrequent, and hence highly stochastic, event. Our results, using a population of 1000, therefore offer an optimistic estimate of the probability for prevention of re-establishment, and make predictions at very low IIRs problematic. Also, our models assume perfect mixing within each mosquito population across all humans. Patch models may offer a way forward to more accurately capture the phenomena of heterogeneity in interactions, as well as spatial heterogeneity in transmission.

The probability that transmission remains interrupted or conversely, re-establishes, is also likely a function of geographical and temporal heterogeneities in importation of infections. We assume that imported infections mix uniformly with the simulated population and enter at a constant rate; however, in reality, individuals bringing malaria infections into an area may concentrate in a particular place. If this effect is important, we expect transmission to spread more slowly, and to be easier to arrest, provided that such foci can be located. Also, rates of case importation may not be constant over time. Our models could incorporate this, but refining these assumptions would require temporal data on human migration patterns. This is an important area of further research (Rebaudet et al., 2010; Tatem and Smith, 2010).

Our rapid method of interrupting transmission likely had an effect on chances of maintaining interruption, as even with the model variants which capture immunity decay, immunity levels remained relatively high in the population for a certain time. In reality, interruption of transmission would take longer and immunity would be lower upon its achievement, resulting in a higher proportion of secondary (locally transmitted) infections manifesting clinically. The level of immunity in the population at the time of interruption, which drives the proportion of infections in the population which are asymptomatic, is an important determinant of the probability of success in preventing re-establishment. This may lead our models to overestimate the probability of re-establishment of transmission.

On the other hand, our method of importing infections may have led us to underestimate the probability of re-establishment of transmission. We assign imported infections randomly to individuals in the simulated population, who are exposed to the same transmission and therefore have the same immunity profile. However, it is likely that transmission in source areas is substantially higher than in the simulated population, and thus individuals importing infections would be expected to have higher immunity. Our current models do not offer the possibility to simulate this immunity differential readily; however, if this were the case we could expect a lower probability that imported infections are symptomatic and therefore detectable by the case management system.

There is a need to extend these models to capture other features of real health systems (Checchi et al., 2006; Kiszewski and Teklehaimanot, 2004; Najera et al., 1998). It would be important to assess the importance of the capacity of the system to react to outbreaks by temporarily improving case management coverage or by implementing emergency vector control operations when outbreaks occur. In countries which succeed in actively interrupting transmission, the health system will likely have strong surveillance and epidemic response capacity, which could contain outbreaks and reduce local transmission again to zero. Screening of potential asymptomatic carriers would likely be a part of this response and was not modeled here. It is also possible that, following interruption of transmission, the case management system would be strengthened to enable more intensive routine detection of cases. Under these conditions, interruption of transmission would be more likely to be maintained, but probability of success would, again, depend to a great degree on the immunity profile of the population concerned.

The case management model offers a very simple description of the health system and does not consider diagnosis, provider practices or patient behaviour which could alter coverage. For a better understanding of the role of case management in achievement and maintenance of transmission interruption, a more realistic case management model is needed.

Thus, there remains a significant unfinished research agenda to increase the understanding of the relationship between case management coverage, vulnerability, receptivity and prevention of re-establishment of *P. falciparum* malaria transmission. Nevertheless, we believe that the results described here provide important input into the discussions surrounding the feasibility of maintaining interruption of malaria transmission in various contexts.

Conclusion

Even at rather low levels of receptivity, case management alone cannot reliably prevent re-establishment of *P. falciparum* malaria transmission in the face of medium to high importation rates, even if all clinical cases are treated. Thus, if vector control is to be discontinued, preventing the importations by controlling transmission in areas from which imported cases originate is a precondition for preventing reintroduction in such settings. Achieving very high levels of case management coverage does not appear to substitute for this. Alternatively, a system of active surveillance to prevent importation, including screening of all potential carriers at points of entry, could be considered, but in most areas this strategy is not likely to be feasible.

Model variants assuming decay of natural immunity resulted in lower odds of transmission re-establishment, relative to the base model that assumed no such decay. These findings highlight the urgent need for research into the mechanisms and rate at which naturally acquired immunity to *P. falciparum* malaria decays in the absence of exposure, to inform current and future malaria elimination efforts. Certain characteristics of the population, in particular heterogeneities in co-morbidity and access to treatment, also appeared to influence simulated probability of success. There is a need for further analysis of effects of different population sizes and patterns of within-population interaction and of geographical and temporal heterogeneity of imported infection rates.

A key issue that has not been addressed here is the related economic analysis. Interruption of transmission and prevention of re-establishment, whether through increased case management coverage or other strategies, will carry significant costs, which need to be evaluated together with appropriate outcome measures and compared to other possible uses of funds to optimize resource use. A recent study found that malaria elimination is unlikely to be cost-saving in most cases, even over a time frame of 50 years, but may bring additional benefits that would make it a worthy investment (Sabot et al., 2010).

The costs and effects of screening asymptomatic individuals, either in response to a detected case or indiscriminately in at-risk populations, will likely need to be considered in addition to case management. Data from field studies are needed to determine the most cost-effective surveillance and response models in different settings and to inform future modeling efforts (Moonen et al., 2010). Importantly, the costs of surveillance are unlikely to increase linearly with coverage; isolated or marginalized populations are usually the last to be reached and the most expensive to serve, resulting in significant diseconomies of scale at the higher coverage levels. In addition, the appropriate outcome measure to use in settings where malaria burden is already very low, as would be the case in places which are close to or have recently achieved elimination, is unclear. Further methodological developments to quantify the benefits of transmission interruption are needed to apply economic evaluation usefully.

The results of these analyses need to be taken into account in global and national discourse and in feasibility assessments of and planning for elimination of malaria (Malaria Elimination Group, 2009). Failure to plan for prevention of re-establishment could result in loss of the last decade's tremendous gains towards rolling back malaria.

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